UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,930	03/22/2004	Sergey Anatolievich Lukyanov	CLON-094	2888

24353 7590 06/01/2006

BOZICEVIC, FIELD & FRANCIS LLP
1900 UNIVERSITY AVENUE
SUITE 200
EAST PALO ALTO, CA 94303

EXAMINER	
MONDESI, ROBERT B	
ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/806,930	LUKYANOV, SERGEY ANATOLIEVICH	
	Examin r	Art Unit	
	Robert B. Mondesi	1653	

-- Th MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 17-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 17-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the amendment filed April 26, 2006. **Claims 11-16** have been canceled. **Claims 27-30** are new. **Claims 1-10 and 17-30** are presently pending and under examination.

Claim of Benefit

In regards claim of benefit to non-provisional application No. 09/976,673 filed October 12, 2001 applicants assert that Non-provisional application 09/976,673 provides on page 35, lines 24-29, and Figures 12 and 13, a working example describing a nucleic acid encoding the polypeptide Cr-44-9. The Cr-44-9 polypeptide comprises a first and a second chromo/fluorescent domain as required by **Claim 1** of the present application. Moreover, as noted on page 17, lines 10 to 16, the chromo/fluorescent domains are derived from *Heteractis crispa*, which is a *Cnidarian* species.

Applicants' arguments have not been found persuasive, because nowhere in the non-provisional application No. 09/976,673 is a description that is supportive of the claimed subject matter that satisfies the requirements of written description under 35 U.S.C 112, first paragraph. In the specification of application No. 09/976,673, there is no mention of a nucleic acid product that encodes a polypeptide which has a first and second fluorescent domain that oligomerize under intracellular conditions. The only reference to any oligomerization-taking place is on page 9, lines 15-20 wherein it is

stated, "of particular interest are oligomerization mutants that do not oligomerize under intracellular conditions".

Furthermore, *Heteractis crispa* is a species of the family *Stichodactylidae*, which is discussed and has support in the non-provisional application No. 09/976,673; however **claims 3-5 and 19-21** are drawn to *Cnidarian* and *Anthozoan* species which are much broader taxonomy classifications and include many more species. For instance *Cnidarian* is a phylum, which contains many classes such as *Hydrozoan* and *Anthozoan*. The class of *Anthozoan* contains several sub classes that themselves contain a variety of orders. The order of *Scleractinia*, which resides in the subclass of *Hexacorallia* and contained in the Class of *Anthozoan*, contains 256 species - one of which would be comparable in classification to *Heteractis crispa*.

Therefore *Heteractis crispa* is of a very narrow scope and does not provide support for the extensively broad scope of a phylum such as *Cnidarian*.

When applicant files a continuation-in-part whose claims are not supported by the parent application, the effective filing date is the filing date of the child CIP. Any prior art disclosing the invention or an obvious variant thereof having a critical reference date more than 1 year prior to the filing date of the child will bar the issuance of a patent under 35 U.S.C. 102 (b). *Paperless Accounting v. Bay Area Rapid Transit System,* 804 F.2d 659, 665, 231 USPQ 649, 653 (Fed. Cir. 1986).

Withdrawal of Objections and Rejections

The objections and rejections not explicitly restated below are withdrawn.

Maint nance of rejections

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1-10 and 17-26 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids (SEQ ID NO:s 3, 5, 7 and 9) encoding tandem chromo/fluorescent polypeptides Cr-44-9 tandem (SEQ ID NO: 4) HcRed2A tandem (SEQ ID NO: 6), M355NA tandem (SEQ ID NO:8), DsRed2-tandem (SEQ ID NO: 10) does not reasonably provide enablement for all nucleic acids encoding polypeptide products comprising a first chromo/fluorescent domain and second chromo/fluorescent domain, wherein said first and second chromo/fluorescent domains are oilgomeric and oilgomerize under intracellular conditions so that the said polypeptide assumes a tertiary structure; including nucleic acids that encode polypeptides wherein the first and second chromo/fluorescent domains are chromo/fluorescent domains from *Cnidarian* or *Anthozoan* species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-10 and 17-26 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Response to applicants' arguments

In regards to the rejection of **claims 1-10 and 17-26** under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acids (SEQ ID NO:s 3, 5, 7 and 9) encoding tandem chromo/fluorescent polypeptides Cr-44-9 tandem (SEQ ID NO: 4) HcRed2A tandem (SEQ ID NO: 6), M355NA tandem (SEQ ID NO:8), DsRed2-tandem (SEQ ID NO: 10) does not reasonably provide enablement for all nucleic acids encoding polypeptide products comprising a first chromo/fluorescent domain and second chromo/fluorescent domain, wherein said first and second chromo/fluorescent domains are oilgomeric and oilgomerize under intracellular conditions so that the said polypeptide assumes a tertiary structure; including nucleic acids that encode polypeptides wherein the first and second chromo/fluorescent domains are chromo/fluorescent domains from *Cnidarian* or *Anthozoan* species, applicants assert that the specification provides ample disclosure to enable one skilled in the art to practice the claimed invention, For example, the subject nucleic acids are described, for example, on page 9, line 3 through page 17, line 15, the particular linked chromo/fluorescent domains aspect is described, for example, on page 10, line 18 though page 12, line 7, exemplary methods of producing such nucleic acids are described, for example, on page 37, line 19 through page 39, line 18, resulting exemplary nucleic acids encoding linked chromo/fluorescent domains are described and, for example, on page 37 and Figures 1-5, constructs, vectors, expression cassettes, and expression systems including the subject nucleic acids are described, for example, on page 15, line 16, through page 17, line 25, and applications using the

subject proteins are described, for example, on page 28, line 17, though page 36, line 20.

Applicants assert further that in maintaining this rejection, the Office Action has focused on the scope of the claims and asserts that the specification does not enable any polypeptides. However, as detailed above, the specification describes multiple different species of fluorescent proteins from *Cnidarian* species. In addition, the specification also describes in great detail several examples of such nucleic acids, including Cr-44-9 (SEQ ID NOs2 1 and 2), HcRed-cr-l (SEQ ID NOs: 5 and 6), AsRed-35-5NA (SEQ IN NOs: 7 and 8), AsRed-35-5D (SEQ ID NOs: 9 and 10) (page 37 and Figures 1-5).

Applicants also assert that the Office action also cites several references as casting doubt with respect to the enablement of the present invention. However, the applicants respectfully disagree. The references cited in the Office action are directed to either hybrid gene encoding a fusion protein of the N-terminal part of dsFP593 and the C-terminal part of drFP583 (Fradkov et al.) or the oligomerization propeties of DsRed (Baird et al.). Therefore, the cited references do not provide any support for the position that the present invention is not enabled because they provide no disclosure as to why the claimed invention would not work as described in the present application. In addition, the references cited in the Office Action do not cast doubt as to the enablement of the claimed invention because the applicants have successfully shown specific examples that have the recited properties.

Applicants' arguments have not been found persuasive. The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan and the guidance presented in the instant specification and the prior art of record. The Applicants make and test position is inconsistent with the decisions of *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) where it is stated that "... scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands*, 858 F.2d at 737, 8 USPQZd at 1404 (Fed. Cir. 1988). Therefore, for the instant specification to be enabling, it needs to provide direction/guidance regarding an acceptable number of different nucleic acids encoding polypeptides comprising the mentioned domains. The nature of "linked oligomeric tertiary structure", as defined by the applicants is considered to be unknown according to the prior art and at best considered to be unpredictable. The molecular biology methods disclosed in the specification of the present application, may be considered to be routine and hence can be practiced by a person skill in the art, however the experimentation required to answer fundamental questions with regards to the scope of the invention can not be considered routine. The reason behind the citation of the noted prior art is for this exact reason, applicants are reminded as claimed, the breadth of the invention encompasses any nucleic acid molecule that encodes a first chromo/fluorescent domain that is linked to by a linking

domain to a second chromo/fluorescent domain, wherein said first and second chromo/fluorescent domain oligomerizes under intracellular conditions so that encoded polypeptide assumes a linked oligomeric tertiary structure. Baird et al., 2000 clearly indicates that oligomerization is a phenomenon unique to certain chromo/fluorescent domains, for example that of DsRred, however it is not a given that anytime two independent chromo/fluorescent domains are linked, oligomerization in view of tertiary structure will take place. This is clearly unique to the construct developed by the applicants and not to all linked chromo/fluorescent domains, therefore the claims should be commensurate with the scope of enablement provided by the applicants in the specification of the present application, namely the disclosed nucleic acid species (SEQ ID NO:s 3, 5, 7 and 9) encoding tandem chromo/fluorescent polypeptides Cr-44-9 tandem (SEQ ID NO: 4) HcRed2A tandem (SEQ ID NO: 6), M355NA tandem (SEQ ID NO:8), DsRed2-tandem (SEQ ID NO: 10).

In regards to the rejection of the **claims 1-10 and 17-26** under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention, applicants assert that as provided in greater detail in the specification on page 9, the tertiary structure of the encoded polypeptide is a result of the oligomerization of the first chromo/fluorescent domain and the second chromo/fluorescent domain. The resulting tertiary structure of the polypeptide is an oligomeric tertiary structure and therefore in the spirit of expediting prosecution and without conceding to the correctness of the rejection, **Claims 1 and 17** have been amended for clarity to recite that the first and second chromo/fluorescent

domains are "linked by a linking domain" and that the "encoded polypeptide assumes a linked oligomeric tertiary structure".

Applicants' arguments have not been found persuasive, because the amendment to the claim does not remedy the deficiencies of the rejected claims under 35 U.S.C. 112, second paragraph. As discussed in Office action mailed January 27, 2006 the mentioned claim language fails to make sense to a person skill in the art and is repugnant to the accepted understating of oligomerization of peptides and tertiary structure in the art. Oilgomerization is a phenomenon that is defined to occur between two or more peptides or polypeptide subunits (monomers). In biochemistry oligomerization occurs between two or more subunits to form a protein complex (see Answers.com publication cited in PTO-892, mailed January 27, 2006). These mentioned subunits are peptides (monomers) that already have a tertiary structure and they are not domains that help form the tertiary structure of a given peptide. Applicants' definition of "linked" oilgomeric "tertiary" structure, on page 9, lines 14-18 does not shed light on the claimed invention or further clarify the claim language.

New Objection(s) and Rejection(s)

Claim Rejections - 35 USC § 102

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-2, 6-10, 17-18 and 22-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Craig et al., United States Patent No. 6,465,199.

Craig et al. teach that one can take advantage of the FRET exhibited by a natural binding domain and its binding partner labeled with different fluorescent protein labels, wherein one is linked to a donor and the other to an acceptor label, in monitoring protein modification according to the present invention. A single polypeptide may comprises a blue fluorescent protein donor label and a green fluorescent protein acceptor label, wherein each is fused to a different assay component (i.e., in which one is fused to the natural binding domain and the other to its binding partner); such a construct is herein referred to as a "tandem" fusion protein (Column 19, lines 10-20).

Craig et al. teach further that The construction and use of tandem fusion proteins in the invention can reduce significantly the molar concentration of peptides necessary to effect an association between differentially-labeled polypeptide assay components relative to that required when single fusion proteins are instead used. The labeled natural binding domain, sequence or polypeptide and/or its binding partner may be produced via the expression of recombinant nucleic acid molecules comprising an in-frame fusion of sequences encoding a such a polypeptide and a fluorescent protein label either in vitro (e.g., using a cell-free transcription/translation system, as described below, or instead using cultured cells transformed or transfected using methods well known in the art) or in vivo, for example in a transgenic animal including, but not limited to, insects, amphibians and mammals. A recombinant nucleic acid molecule of use in the invention may be constructed and expressed by molecular methods well known in the art, and may additionally comprise sequences including, but not limited to, those which encode a tag (e.g., a histidine tag) to enable easy purification, a secretion signal,

a nuclear localization signal or other primary sequence signal capable of targeting the construct to a particular cellular location, if it is so desired (Column 19, lines 24-46).

Craig et al. also teach that recombinant nucleic acid constructs of particular use in the invention are those which comprise in-frame fusions of sequences encoding a natural binding domain or a binding partner therefor and a fluorescent protein. If a natural binding domain and its binding partner are to be expressed as part of a single polypeptide, the nucleic acid molecule additionally encodes, at a minimum, a donor fluorescent protein label fused to one, an acceptor fluorescent protein label fused to the other, a linker that couples the two and is of sufficient length and flexibility to allow for folding of the polypeptide and pairing of the natural binding domain, sequence or polypeptide with the binding partner, and gene regulatory sequences operatively linked to the fusion coding sequence (Column 21, lines 25).

Craig et al. also teach that a "fluorescent tag", "fluorescent label" or "fluorescent group" refers to either a fluorophore or a fluorescent protein or fluorescent fragment thereof. "Fluorescent protein" refers to any protein which fluoresces when excited with appropriate electromagnetic radiation. This includes proteins whose amino acid sequences are either natural or engineered. A "fluorescent protein" is a full-length fluorescent protein or fluorescent fragment thereof. By the same token, the term "linker" refers to the radical of a molecular linker that is coupled to both the donor and acceptor protein molecules, such as an amino acid sequence joining two natural binding domains, sequences or polypeptides or joining a natural binding domain, sequence or polypeptide and its corresponding binding partner, or a disulfide bond between two

polypeptide sequences, whether the sequences are present on the same- or on different polypeptide chains (Column 9, lines 35-49).

Craig et al. also teach that in order to facilitate convenient and widespread use of the invention, a kit is provided which contains the essential components for screening the activity of a an enzyme which mediates a change in protein modification, as described above. A labeled, natural binding domain, sequence or polypeptide, as defined above, and a differentially labeled binding partner which binds it specifically in a modification-dependent manner is provided, as is a suitable reaction buffer for in vitro assay or, alternatively, cells or a cell lysate. A reaction buffer which is "suitable" is one which is permissive of the activity of the enzyme to be assayed and which permits modification dependent binding of the natural binding domain, sequence or polypeptide and the binding partner. The labeled components are provided as peptide/protein or a nucleic acid comprising a gene expression construct encoding the one or more of a peptide/protein (Column 47, lines 28-44).

Thus Craig et al. teach all the elements of **claims 1-2, 6-10, 17-18 and 22-26** and these claims are anticipated under 35 USC 102(e).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 3-6 and 19-21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Craig et al., United States Patent No. 6,465,199 in view of Fradkov et al., 2000 (Cited in the IDS filed June 23, 2004).

Craig et al. disclose a nucleic acid molecule as stated above.

Craig et al. do not disclose that the chromo/fluorescent domains are chromo-or fluorescent domains from a non-bioluminescent *Anthozoan* species.

Fradkov et al. disclose chromo-or fluorescent domains from a non-bioluminescent *Anthozoan* species (Abstract and page 130, Fig 3.).

Fradkov et al. teach that ds/drFP616 (chromo-or fluorescent domain from a non-bioluminescent *Anthozoan* species) is the most red shifted fluorescent protein to date and its unique specteral properties are promising for different biological applications, for instance it could become the most appropriate partners for GFPs in double a triple labeling systems the longer wavelength and virtual absence of excitation in the green spectral band should preclude any spectral overlap and background fluorescence which allows simultaneous detection of red and green fluorescent proteins *in vivo* (Page 130, column 2, paragraph 3, lines 1-9).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use chromo-or fluorescent domain from a non-bioluminescent *Anthozoan* species in a tandem fusion protein construct for the advantages of double or triple labeling systems, virtual absence of excitation in the green spectral band, the exclusion of spectral overlap and background fluorescence which allows simultaneous

detection of red and green fluorescent proteins as taught by Craig et al. and Fradkov et al., see Fradkov et al. at (Page 130, column 2, paragraph 3, lines 1-9).

Claims 27-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Craig et al., United States Patent No. 6,465,199 in view of Fradkov et al., 2000 (Cited in the IDS filed June 23, 2004) and Guegler et al. United States Patent No. 6,326,175.

Craig et al. and Fradkov et al. disclose a nucleic acid molecule as stated above.

Craig et al. and Fradkov et al. do not teach that the nucleic acid molecule of the invention encodes a polypeptide that comprises a linking domain that is from about 1 to about 5 residues in length.

Guegler et al. disclose a nucleic acid molecule that encodes a fusion polypeptide that comprises a linking domain that is from about 1 to about 5 residues in length.

Guegler et al. teach that the linker domain is a flexible linker that is of sufficient length to provide for substantially free movement of the two eIF domains relative to each other. Because of the manner in which the fusion protein is produced, the linker domain is a stretch of amino acids, where the stretch of amino acids is generally at least about 5 aa in length. The amino acid sequence of the linking domain may be any convenient sequence, as long as the sequence does not give rise to some stable secondary structure that may diminish the flexibility of the domain (Column 3, lines 63-67 through column 4, lines 10).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a linker domain that is about 1 residue to about 5 residues in lenght in a tandem fusion protein construct for the advantages of a linker domain that is

a flexible linker and is of sufficient length to provide for substantially free movement of the linked proteins as taught by Craig et al., Fradkov et al. and, see Guegler et al. at column 3, line 64-66).

Conclusion

No claims are allowed

Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert B Mondesi whose telephone number is 571-272-0956. The examiner can normally be reached on 9am-5pm, Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Weber
Supervisory Patent Examiner

Robert B. Mondesi
Patent Examiner
Group 1653

Robert B. Mondesi
5-23-06